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EDITORIAL COMMENT

A Microvascular-Myocardial Diastolic Dysfunctional State and Risk for Mental Stress Ischemia

A Revised Concept of Ischemia During Daily Life*

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To improve our understanding of pathophysiological responses to stress in "triggering" adverse events, stressors have been used in the laboratory to evoke "mental stress–induced ischemia" (MSIMI). Our studies found that patients with MSIMI had increased risk for death (1), and their hemodynamic and neurohormonal changes differed from those observed with exercise (2). Mental stress increased heart rate, systolic blood pressure, cardiac output, and systemic vascular resistance, which correlated with plasma epinephrine increases, whereas during exercise-induced ischemia, systemic resistance declined, with no relationship to epinephrine levels. Interestingly, depression of left ventricular (LV) ejection fraction (EF) was greater with MSIMI than with exercise and was inversely correlated with systemic resistance. Greater increases in epinephrine and norepinephrine occurred during exercise, whereas greater increases in systemic resistance occurred with MSIMI. Thus, arteriolar constriction and minor increases in myocardial oxygen demand occur with MSIMI compared with exercise as adrenal epinephrine secretion mediates, in part, these different responses. Our findings provide a framework for the underlying pathophysiological processes involved in responses to mental stress.

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Hypothetical Mechanistic Construct for Mental Stress Ischemia

The prevailing model suggests that MSIMI results from coronary microcirculatory dysfunction (limited dilation and/or constriction) in the setting of endothelial and/or vascular smooth muscle dysfunction (Fig. 1). Atherosclerosis risk conditions (hypertension, dysglycemia, etc.), via oxidant stress and inflammation, and dysregulation of the central nervous system and hypothalamic-pituitary-adrenal axis likely contribute. The pathophysiological mechanisms of MSIMI are also important in understanding daily-life ischemia, elucidating links with adverse outcomes, and providing direction for appropriate management.

In this issue, Ersbøll et al. (3) report that patients with MSIMI have LV dysfunction in the absence of the mental stress test. This finding suggests that a more chronic form of asymptomatic ischemia is present during their daily lives, extending concepts of the "silent" ambulatory electrocardiographic and LV perfusion abnormalities that we described several decades ago (4,5).

Some Thoughts on the Left Ventricular Dysfunction Observed in Subjects With Mental Stress–Induced Ischemia

It is suspected that stress over time leads to a microvascular-myocardial diastolic dysfunctional state. The pattern of LV dysfunction from microvascular dysregulation is different from that observed with obstructive epicardial coronary disease. The latter initially leads to impaired regional LV relaxation reflected in global relaxation measures and later impaired contraction. Our cardiac magnetic resonance studies indicated that ischemia resulting from

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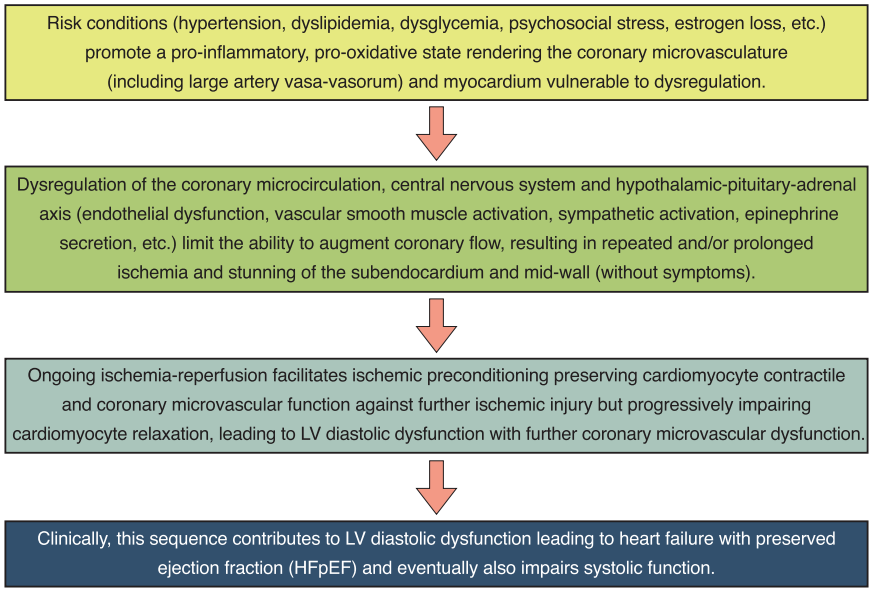

Figure 1. Microvascular Ischemia Hypothesis With or Without Obstructive Atherosclerosis

The prevailing model suggests that mental stress ischemia results from coronary microcirculatory dysfunction (limited dilation and/or constriction) in the setting of endothelial and/or vascular smooth muscle dysfunction. LV = left ventricular.

microvascular dysregulation appears more diffuse but limited to the subendocardium and midwall, with less profound functional alterations.

LV diastolic dysfunction is prevalent in patients with endothelial dysfunction, related to microvascular inflammation or dysregulation, and this likely contributes to heart failure with preserved EF (HFpEF) (6). Although patients with HFpEF have relatively normal EFs, mild systolic dysfunction is not readily detectable with global EF. Parameters used to evaluate LV function in patients with MSIMI and microvascular dysregulation may require constructs derived from measures of diastolic and systolic LV function.

Ersbøll et al. (3) used a composite LV function score, the eas index ($e'/a' \times s'$), which includes both diastolic and systolic measures of mitral annular longitudinal motion. This index incorporates information about systolic dysfunction with increased preload (e'/s') and increased LV stiffness (e'/a'), and a high eas index indicates increased preload with systolic dysfunction, diastolic dysfunction, or both (7). Patients in the present study had MSIMI but also had increased eas indexes at baseline without the mental stressor, suggesting mild diastolic dysfunction. With advanced diastolic dysfunction, e' would continue to decrease and may become out of proportion to the decrease in a' or s', which could lead to reduction in the eas index (8). Although consideration of systolic and diastolic LV function in MSIMI and microvascular dysregulation is important, correlation of eas index with clinical outcomes in patients with MSIMI with more severe LV diastolic dysfunction remains warranted.

Importantly, the eas index evaluates both systolic and diastolic longitudinal LV motion, a critical aspect of efficient contraction (9). Longitudinal motion depends primarily on subendocardial fiber contraction, and deficits in longitudinal contraction are an early marker of damage related to ischemia and/or subendocardial fibrosis in pressure overload (10). Longitudinal contractility is reduced in patients with HFpEF (11). Longitudinal contractility appears to be an appropriate measure of LV function in patients with MSIMI.

Considerations on Need to Revise the Prevailing Microvascular Ischemia Model

First, these patients had ischemia at other times in response to a mental stressor, and their microvasculature and myocardium were likely "vulnerable" to stressors in daily life. One such stressor may be the baseline echocardiographic procedure per se.

Second, such vulnerable patients likely have similar ischemia-related LV functional changes off and on or persisting chronically. If proved, this would require a

revision of long-held concepts of chronic ischemic heart disease whereby ischemic episodes are believed to be of relatively brief duration (e.g., transient). However, an exception is myocardial stunning, for example, persisting long after catecholamine-induced ischemic episodes (12). With the latter process, LV dysfunction may require considerable time to recover. Within the coronary microvascular dysfunction framework, a revised concept of more or less continuing ischemia-related LV alterations or stunning would involve smaller, patchy areas of cardiomyocyte dysfunction. This might also explain stress-induced cardiomyopathy and HFpEF.

Third, it is likely that increased pulsatile LV loading with mental stress affects LV function (13). Increased arterial stiffness is an important determinant of myocardial blood flow and may alter microvascular flow, similar to an obstructive epicardial coronary stenosis. As we have noted (14), at any arterial pressure, subendocardial perfusion is dependent on the ratio of time the left ventricle is in diastole and cardiac cycle duration: diastolic pressure time fraction (DPTF) (15,16). This represents the duration without compression of intramural microvessels during contraction critical for adequate LV perfusion (17). Our study participants, with symptoms or signs of ischemia without epicardial coronary obstruction, had longer ejection durations compared with a reference group. This prolonged ejection duration decreased diastolic pressure time and DPTF, indicating reduced subendocardial blood supply. This adverse change, coupled with the increase in LV afterload, causes a mismatch in ventricular-vascular coupling and an imbalance in the supply/demand ratio. This contention is supported by reduction in both DPTF/systolic pressure time fraction and the myocardial viability ratio (14). This scenario may result in ischemia at a lower workload, even in individuals without obstructed epicardial coronary arteries (15–18). In patients with ischemic heart disease and nonobstructed coronary arteries, DPTF is lower at rest and during exercise compared with normal control subjects (18). Indeed, a decrease in DPTF can have the same effect as an increase in epicardial coronary stenosis. Furthermore, patients with ischemic heart disease without obstructed coronary arteries often have endothelial and/or microvascular dysfunction (19,20). These dynamic loading changes are influenced by many components of daily life, including mental stress.

Opportunities for Cardiovascular Imaging

The links between MSIMI and the course of coronary microvascular and myocardial defects, over time, are needed. To this end, Doppler echocardiographic perfusion studies with coronary microvascular spasm have promise (21). Cardiac magnetic resonance with gadolinium perfusion has yielded considerable information. Finally, explorations of underlying mechanisms, markers and mediators reflecting nervous system activation, hormonal status, endothelial and vascular smooth muscle function, and inflammation and myocardial infiltration (scar, fat, and so on) would be helpful.

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